

REDUCTION OF AROMATIC NITROALKENES WITH BAKER'S YEAST

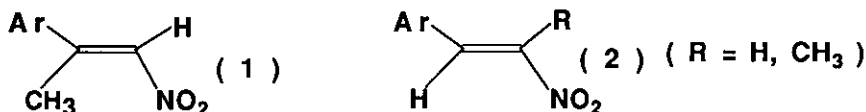
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Abstract—Aromatic nitroalkenes were reduced chemoselectively with baker's yeast to give the corresponding nitroalkanes.

It is widely recognized that nitro compounds are useful in synthetic organic chemistry because of the easiness to convert into other compounds such as amines or ketones.¹ Among the syntheses of nitro compounds, nitroalkanes were prepared enzymatically from nitroalkenes in some cases.^{2,3} In the reaction of 1-nitro-2-phenylpropene (**1**) with baker's yeast,² carbon-carbon double bond was reduced to give the corresponding nitroalkanes. However, few papers on the enzymatic reduction of aromatic nitroalkenes have been reported.⁴ Herein, we would like to report the chemoselective reduction of heteroaromatic nitroalkenes with baker's yeast.

For extension of chemoselective reduction of *E*- β -nitrostyrene derivatives (**2**), we examined the influences of the substituent on the aromatic ring for the enzymatic reduction.



As shown in Table I, fermentation of *E*- β -nitrostyrenes (**3 a-o**) with baker's yeast at 31-33 °C for 72-74 h gave the corresponding nitroalkanes (**4 a-o**) in 28-81% chemical yields. In these reactions, it was found that when an electron-withdrawing group such as Br, Cl and CN (**3 i-o**) was substituted on the aromatic ring, chemical yields of *meta*- or *ortho*-substituted compounds were higher than those of *para*-substituted

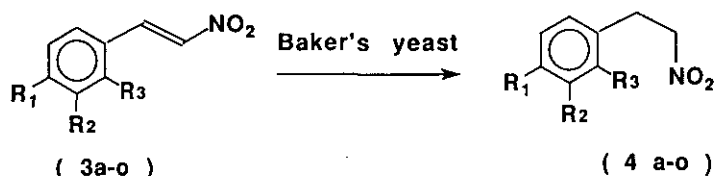
Dedicated to Professor Aran. R. Katritzky on the occasion of his 65th birthday.

compounds. But, distinct differences in reducibilities between an electron-donating group substituted compounds (**3b-h**) and electron-withdrawing group substituted compounds (**3i-o**) were slightly observed. (Table I)

The same reaction of methyl substituted *E*- β -nitrostyrene (**5a-n**) with baker's yeast also proceeded smoothly to give nitroalkanes (**6a-n**) in 42-73% chemical yields, although the optical rotations of the products were low because of racemization.³ (Table II)

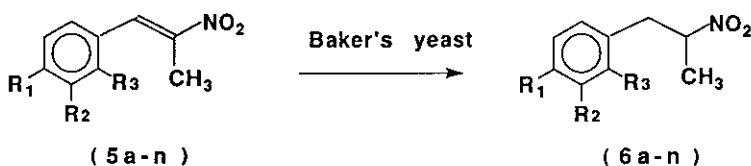
Interestingly, when a nitro group substituted on the benzene ring (**7a-c**), selective reduction, as we reported previously,⁵ took place to give nitroalkane (**8a-c**) in 42-65% chemical yields accompanied with amino derivatives (**9a-c**) as minor products (0-5% chemical yields). In contrast, when methyl substituted nitroalkenes (**7 d-f**) were treated with baker's yeast under the same conditions, amino derivatives (**9d-f**) were obtained (61 and 16 %) in preference to nitroalkane (**8d-f**) (24 and 10%).

Table I. Reduction of *E*-Nitro Alkenes with Baker's Yeast



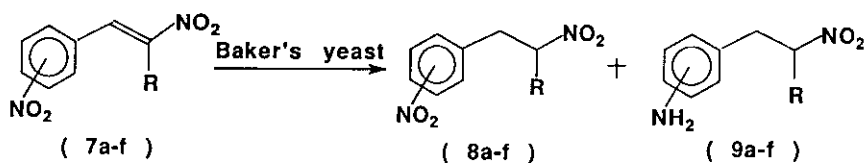
(3)				Temp °C	Time h	(4)		(3)				Temp °C	Time h	(4)	
	R ₁	R ₂	R ₃			Yield (%)			R ₁	R ₂	R ₃			Yield (%)	
3a^{a,b}	H	H	H	31	72	43 ^{h,i}		3j^{p,q,f}	CN	H	H	31	74	28 ^{a,f}	
3b^{a,c,d}	CH ₃ O	H	H	33	74	75 ^{c,h}		3k^d	H	CN	H	31	73	69	
3c^{a,d}	H	CH ₃ O	H	33	74	81 ^j		3lⁱ	Br	H	H	33	74	46 ^m	
3d^a	H	H	CH ₃ O	33	74	57 ^h		3m^g	H	Br	H	33	74	52	
3e^{b,d}	CH ₃	H	H	32	72	67 ^{c,j,k}		3n^d	H	H	Br	33	74	61	
3f^b	H	CH ₃	H	32	72	41		3o^{a,b}	Cl	H	H	31	73	67 ^{c,k,n}	
3g^b	H	H	CH ₃	33	73	73 ⁱ									
3h^a	OH	H	H	33	74	37 ^k									

a) see ref. 6a. b) see ref. 6b. c) see ref. 6c. d) see ref. 6d. e) see ref. 6e. f) see ref. 6f.
 g) see ref. 6g. h) see ref. 4. i) see ref. 6h. j) see ref. 6i. k) see ref. 6j. l) see ref. 6k.
 m) see ref. 6l. n) see ref. 6n.

Table II. Reduction of *E*-Aryl-2-nitropropenes with Baker's Yeast

(5)				Temp. °C	Time h	(6)	(5)				Temp. °C	Time h	(6)
	R ₁	R ₂	R ₃			Yield (%)		R ₁	R ₂	R ₃			Yield (%)
5a ^{a,b}	H	H	H	24	120	79 ^k	5h ^{e,f}	CN	H	H	33	65	48 ^g
5b ^{a,b,c,d}	CH ₃ O	H	H	33	75	42 ^{k,l}	5i	H	CN	H	33	67	52
5c ^{a,c,f}	H	CH ₃ O	H	33	50	60 ^l	5j ^{a,f,j}	Cl	H	H	33	64	73 ^c
5d ^{c,f,g}	CH ₃	H	H	33	71	61 ^l	5k ^a	H	Cl	H	33	50	42 ^c
5e ^{a,c}	H	CH ₃	H	33	48	59 ^l	5l ^{i,j}	H	H	Cl	33	50	48 ⁿ
5f ^h	H	H	CH ₃	33	71	69 ^l	5m	H	Br	H	33	69	52 ^o
5g ^l	OH	H	H	33	72	69 ^m	5n	H	H	Br	33	70	44 ^o

a) see ref. 7a. b) see ref. 7b. c) see ref. 7c. d) see ref. 7d. e) see ref. 7e. f) see ref. 6b.
 g) see ref. 7g. h) see ref. 6g. i) see ref. 6a. j) see ref. 6h. k) see ref. 4. l) see ref. 7f.
 m) see ref. 3. n) see ref. 6f. o) see ref. 7h.

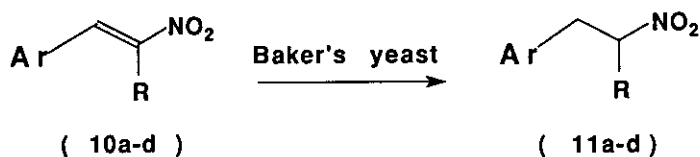
Table III. Reduction of *E*-Nitrophenyl Nitroalkenes with Baker's Yeast

(7)			Temp. °C	Time h	(8)	(9)
	Phenyl	R			Yield (%)	Yield (%)
7a ^a	4-NO ₂	H	33	72	44 ^{a,h}	5 ^h
7b ^a	3-NO ₂	H	33	70	42	0
7c ^a	2-NO ₂	H	33	72	65	0
7d ^{b,c,d}	4-NO ₂	CH ₃	33	72	24 ^{i,j}	61 ⁱ
7e ^{b,d,e}	3-NO ₂	CH ₃	33	72	10 ^j	28
7f ⁱ	2-NO ₂	CH ₃	33	52	24	16

a) see ref. 6a. b) see ref. 7a. c) see ref. 7b. d) see ref. 7d.
 e) see ref. 7e. f) see ref. 8a. g) see ref. 6j. h) see ref. 8b.
 i) see ref. 8c. j) see ref. 7c.

We next applied these enzymatic reduction to heteroaromatic nitroalkenes. When *E*-3-indolyl- or 3-pyridyl nitroalkenes (**10 a-d**) were treated with baker's yeast at 33 °C for 72-109 h, chemoselective reductions occurred to give the corresponding 3-indolyl- or 3-pyridyl nitroalkanes (**11a-d**) (44- 73% chemical yields), while reduction of *E*-*N*-phenyl-3-indolyl nitroethene (**10c**) did not proceed at all.

Table IV. Reduction of *E*-Heteroaromatic Nitroalkenes with Baker's Yeast.

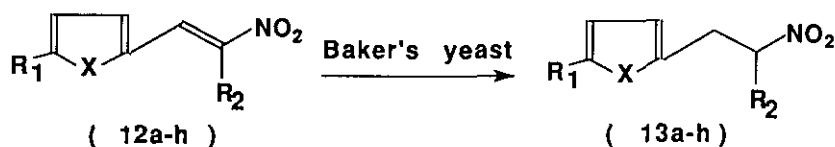


(10)			Temp. °C	Time h	(11)
	Ar	R			Yield (%)
10a ^a	3-Indolyl	H	33	72	44 ^d
10b ^a	3-Indolyl	CH ₃	33	109	65
10c	<i>N</i> -Phenyl-3-indolyl	H	33	72	0
10d ^{b,c}	3-pyridyl	CH ₃	33	72	73

a) see ref. 9a. b) see ref. 7a. c) see ref. 9b. d) see ref. 9c.

When five-membered ring (thiophene, furan, and pyrrol) substituted *E*-nitroalkenes (**12 a-h**) were treated with baker's yeast under the same conditions, carbon-carbon double bonds were selectively reduced to afford the corresponding nitroalkanes (**13a-h**) in 45-79% chemical yields. In the reactions, significant differences in reactivities among five-membered heteroaromatics were not observed. But, to be notice, when a methyl group was substituted on the double bond (**10c, 10d, 12e, 12g, 12h**), the yields of the products were higher than those in the case of unmethylated compounds (**10a-b, 12a, 12c, 12d**). Thus, it was found that heteroaromatic nitroolefins were reduced chemoselectively with baker's yeast to give the corresponding nitroalkanes in moderate to good chemical yields.

Table V. Reduction of *E*-Five-membered Heteroaromatic Nitroalkenes with Baker's Yeast.



(12)				Temp.	Time	(13)
	X	R ₁	R ₂	°C	h	Yield (%)
12a ^{a,b}	S	H	H	33	72	61 ^f
12b ^c	S	Br	H	33	50	79 ^g
12c ^{a,b}	O	H	H	33	50	59 ^f
12d ^b	<i>N</i> -CH ₃	H	H	33	72	45 ^h
12e ^{b,d}	S	H	CH ₃	33	72	75 ^{g,i}
12f ^d	S	Br	CH ₃	33	64	46 ⁱ
12g ^e	O	H	CH ₃	33	72	74 ^g
12h	<i>N</i> -CH ₃	H	CH ₃	33	72	79

a) see ref. 7f. a) see ref. 9a. c) see ref. 10a. d) see ref. 10b.

e) see ref. 9b. f) see ref. 4. g) see ref. 6j. h) see ref. 10c.

i) see ref. 10b.

EXPERIMENTAL

¹H-Nmr spectra were recorded on JEOL PMX-60si (60MHz) or JNM-GMX-400 (400MHz) spectrometers with tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL JMN-DX 303. Melting point were determined on a Yanagimoto melting point apparatus and are uncorrected. For column chromatography, silica gel (Wacogel C-200, from Wako Pure chemical Industries, Ltd.) was used. Configuration of β -nitrostyrenes was confirmed to be *E* by the coupling constant ($J = 14\text{Hz}$) and nOe effect in ¹H-nmr spectra.

General procedure for the reduction of *E*- β -nitrostyrenes (3a-o) with Baker's yeast.

A mixture of *E*- β -nitrostyrenes (3a-o) (0.5 g) and baker's yeast (250 g)(purchased from Oriental Yeast Co.) in water (250 ml) was fermented for 72-74 h at 31-33° C. The mixture was extracted continuously with CHCl_3 using a Soxlet apparatus and the extract was dried over Na_2SO_4 . The solvent was removed under reduced pressure to give the residue which was purified by silica gel (10-15 g) column chromatography using CH_2Cl_2 as eluent to yield 1-aryl-2-nitroethanes (4a-o)(Table I).

3j : a colorless powder, mp 110-112°C($\text{MeOH-Et}_2\text{O}$); $^1\text{H-nmr}$ (CDCl_3) δ : 7.57 (1H, d, J = 14Hz), 7.67-7.99 (5H, m); ms m/z : Calcd. for $\text{C}_9\text{H}_6\text{N}_2\text{O}_2(\text{M}^+)$: 174.0429. Found : 174.0406.

3l : an oil, $^1\text{H-nmr}$ (CDCl_3) δ : 7.16-8.14 (6H, m); ms m/z : Calcd. for $\text{C}_8\text{H}_6\text{BrNO}_2(\text{M}^+)$: 226.9581. Found : 226.9627.

4f : an oil, $^1\text{H-nmr}$ (CDCl_3) δ : 3.33 (3H, s), 3.60 (2H, t, J =7Hz), 4.57 (2H, t, J =7Hz), 7.22-7.80 (4H, m); ms m/z : Calcd. for $\text{C}_9\text{H}_{11}\text{NO}_2(\text{M}^+)$: 165.0790. Found : 165.0784.

4j : an oil, $^1\text{H-nmr}$ (CDCl_3) δ : 3.33 (2H, t, J =7Hz), 4.60 (2H, t, J =7Hz), 7.57 (4H, s); ms m/z : Calcd. for $\text{C}_9\text{H}_8\text{N}_2\text{O}_2(\text{M}^+)$: 176.0586. Found : 176.0613.

4l : an oil, $^1\text{H-nmr}$ (CDCl_3) δ : 3.30 (2H, t, J =7Hz), 4.60 (2H, t, J =7Hz), 7.01-7.73 (4H, m); ms m/z : Calcd. for $\text{C}_8\text{H}_8\text{BrNO}_2(\text{M}^+)$: 228.9738. Found : 228.9801.

4m : an oil, $^1\text{H-nmr}$ (CDCl_3) δ : 3.33 (2H, t, J =7Hz), 4.57 (2H, t, J =7Hz), 6.80-7.87 (4H, m); ms m/z : Calcd. for $\text{C}_8\text{H}_8\text{BrNO}_2(\text{M}^+)$: 228.9738. Found: 228.9700.

General procedure for the reduction of *E*- α -methyl- β -nitrostyrenes (5a-n) with Baker's

yeast. A mixture of *E*- α -methyl- β -nitrostyrenes (5a-n) (0.5 g) and baker's yeast (250 g)(purchased from Oriental Yeast Co.) in water (250 ml) was fermented for 48-120 h at 24-33° C. The mixture was extracted continuously with CHCl_3 using a Soxlet apparatus and the extract was dried over Na_2SO_4 . The solvent was removed under reduced pressure to give the residue which was purified by silica gel (10-15 g) column chromatography using CH_2Cl_2 as eluent to yield 1-aryl-2-nitropropanes (6a-n) (Table II).

5i : a colorless powder, mp 107-109°C ($\text{MeOH-Et}_2\text{O}$); $^1\text{H-nmr}$ (CDCl_3) δ : 2.65 (3H,s), 7.64-7.83 (4H,

m), 8.02 (1H,s); ms m/z : Calcd. for $C_{10}H_8N_2O_2(M^+)$: 188.0586. Found : 188.0592.

5m : an oil, 1H -nmr ($CDCl_3$) δ : 2.75 (3H,s), 7.20-7.90 (4H, m), 7.99 (1H, s); ms m/z : Calcd. for $C_9H_8BrNO_2(M^+)$: 240.9738. Found : 240.9800.

5n : an oil, 1H -nmr ($CDCl_3$) δ : 2.33 (3H, s), 7.17-7.87 (4H, m), 8.15 (1H, s); ms m/z : Calcd. for $C_9H_8BrNO_2(M^+)$: 240.9738. Found : 240.9844.

6i : an oil, 1H -nmr ($CDCl_3$) δ : 1.57 (3H, d, $J=7Hz$), 2.83-3.63 (2H, m), 4.50-5.16 (2H, m), 7.20-7.60 (4H, m); ms m/z : Calcd. for $C_{10}H_{10}N_2O_2(M^+)$: 190.0720. Found : 190.0740.

General procedure for the reduction of *E*-1-Nitrophenyl-2-nitroalkenes (7a-f) with

Baker's yeast. A mixture of *E*-1-Nitrophenyl-2-nitropropenes (7a-f) (0.5 g) and baker's yeast (250 g)(purchased from Oriental Yeast Co.) in water (250 ml) was fermented for 70-72 h at 33° C. The mixture was extracted continuously with $CHCl_3$ using a Soxhlet apparatus and the extract was dried over Na_2SO_4 . The solvent was removed under reduced pressure to give the residue which was purified by silica gel (10-15 g) column chromatography using CH_2Cl_2 as eluent to yield 1-nitrophenyl-2-nitroalkanes (8a-f) and CH_2Cl_2 : MeOH (98 : 2) as eluent to yield 1-aminophenyl-2-nitroalkanes(9a-f)(Table III).

8b : an oil, 1H -nmr ($CDCl_3$) δ : 3.50 (2H, t, $J=7Hz$), 4.73 (2H, t, $J=7Hz$), 7.18-8.34 (3H, m); ms m/z: Calcd. for $C_8H_8N_2O_4(M^+)$: 196.0484. Found : 196.0475.

8c : an oil, 1H -nmr ($CDCl_3$) δ : 3.57 (2H, t, $J=7Hz$), 4.77 (2H, t, $J=7Hz$), 6.98-8.17 (4H, m); ms m/z: Calcd. for $C_8H_8N_2O_4(M^+)$: 196.0484: Found : 196.0473.

8f : an oil, 1H -nmr ($CDCl_3$) δ : 1.63 (3H, d, $J=7Hz$), 3.16 (1H, dd, $J=7, 14Hz$), 3.47 (1H, dd, $J=7, 14Hz$), 4.57-5.17 (1H, m), 7.20-8.27 (4H, m); ms m/z: Calcd. for $C_{10}H_{10}N_2O_2(M^+)$: 210.0641. Found : 210.0601.

9e : an oil, 1H -nmr ($CDCl_3$) δ : 1.50 (3H, d, $J=7Hz$), 2.86 (1H, dd, $J=7, 14Hz$), 3.27 (1H, dd, $J=7, 14Hz$), 4.42-5.10 (1H, m), 6.48-7.23 (4H, m); ms m/z : Calcd. for $C_9H_{12}N_2O_2(M^+)$: 180.0899. Found : 180.0914.

9f : an oil, 1H -nmr ($CDCl_3$) δ : 1.50 (3H, d, $J=7Hz$), 2.89 (1H, dd, $J=7, 14Hz$), 3.27 (1H, dd, $J=7, 14Hz$), 4.51- 5.13 (1H, m), 6.83-7.42 (4H, m); ms m/z : Calcd. for $C_9H_{12}N_2O_2(M^+)$: 180.0899. Found :

180.0886

General procedure for the reduction of *E*-1-Heteroaryl-2-nitroalkenes (10a-d) with

Baker's yeast. A mixture of *E*-1-heteroaryl-2-nitropropenes(10 a-d) (0.5 g) and baker's yeast (250 g)(purchased from Oriental Yeast Co.) in water (250 ml) was fermented for 72 -109 h at 33° C. The mixture was extracted continuously with CHCl_3 using a Soxlet apparatus and the extract was dried over Na_2SO_4 . The solvent was removed under reduced pressure to give the residue which was purified by silica gel (10-15 g) column chromatography using CH_2Cl_2 as eluent to yield 1-heteroaryl-2-nitroalkanes(11a-d) (Table IV).

11d : an oil, ^1H -nmr (CDCl_3) δ : 1.53 (3H, d, $J=7\text{Hz}$), 3.03 (1H, dd, $J=7, 14\text{Hz}$), 3.37 (1H, dd, $J=7, 14$ Hz), 4.50-5.20 (1H, m), 7.15-8.71 (4H, m); ms m/z : Calcd. for $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_2(\text{M}^+)$: 166.0742.

Found : 166.0734.

General procedure for the reduction of Five-membered *E*-Heteroaryl-2-nitroalkenes

(12a-h) with Baker's yeast. A mixture of five-membered *E*-heteroaryl-2-nitroalkenes(12a-h) (0.5 g) and baker's yeast (250 g)(purchased from Oriental Yeast Co.) in water (250 ml) was fermented for 50-72 h at 33° C. The mixture was extracted continuously with CHCl_3 using a Soxlet apparatus and the extract was dried over Na_2SO_4 . The solvent was removed under reduced pressure to give the residue which was purified by silica gel (10-15 g) column chromatography using CH_2Cl_2 as eluent to yield five-membered heteroaryl-2-nitroalkanes(13a-h). (Table V)

12h : pale yellow powder, mp 62-64 °C(EtOH); ^1H -nmr (CDCl_3) δ : 2.50 (3H, s), 3.76 (3H, s), 6.21-7.02 (3H, m), 8.11 (1H, s); ms m/z : Calcd. for $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_2(\text{M}^+)$: 166.0742. Found : 166.0727.

13h : an oil, ^1H -nmr (CDCl_3) δ : 1.56 (3H, d, $J=7\text{Hz}$), 2.90 (1H, dd, $J=7, 14\text{Hz}$), 3.33 (1H, dd, $J=7, 14\text{Hz}$), 4.43-5.01(1H, m), 5.86-6.65(3H, m); ms m/z : Calcd. for $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_2(\text{M}^+)$: 168.0899. Found: 168.0914.

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